FOSTERING COMMUNICATION AND COLLABORATION

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Translational Research

GRIFF RODGERS: CHOREOGRAPHING HEMATOPOIESIS

by Fran Pollner

Speaking of the work he does in the lab and in the clinic, Griff Rodgers uses phrases like "reactivating genes" and "reversing ontogeny." This is not hyperbole. These are essential strategies in the business of deciphering and destabilizing sickle cell disease (SCD)—a prime focus for Rodgers since his arrival at NIH in 1982.

Now NIDDK deputy director and chief of the Clinical and Molecular Hematology Branch, Rodgers' research over the past two decades has advanced the understanding and management of SCD and related thalassemias. His basic and clinical studies established that hydroxyurea, a cancer chemotherapy agent, reactivated the dormant fetal hemoglobin gene in SCD patients, producing a normal red blood cell population and substantial relief from the crippling clinical manifestations of the disease. In 1998, hydroxyurea became the first—and thus far only—drug to gain FDA approval for use in SCD.

Griff Rodgers

Today, he and his team are involved in determining the molecular basis of hydroxyurea's effect.

The methods used in this pursuit are providing a bridge from pharmaceutical to stem cell and genetic approaches to hereditary blood disorders—and to the broader sphere of "regenerative" medicine with hematopoietic stem cells as source

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MIGHTY MACHINES FOR MINI-MODELS: ALL SYSTEMS GO FOR NEW MOUSE IMAGING FACILITY

by Fran Pollner

The mouse has always had a central place in studies of human health and disease; but in the age of the mouse genome and transgenic and knockout mouse models, its standing and ubiquity in basic and clinical research are beyond measure.

Just about everything else in the mouse, however, *is* measurable—and visible in all its aspects, with the right tools.

NIH has now amassed those tools and centralized them in a state-of-the-art home that reflects the status of the mouse in biomedical research.

Fran Pollner

Not the Least Miffed *(l to r): Felix Onojafe, biologist; Daryl Despres, biologist; Brenda Klaunberg, research veterinarian; Alan Koretsky, director; Marty Lizak, MRI physicist; Alan Olson, engineer; Lalith Talagala, technical director*

The Mouse Imaging Facility (MIF), nestled at the end of a labyrinthine series of art-covered corridors in the B1 level of the Clinical Center, is now ready to accommodate NIH's substantial mouse biology community. (It will also be open for general viewing March 5; see "Open House," page 8).

The MIF is an NIH-wide shared resource to which all intramural scientists have access. In 1998, it was an idea whose time had come, pushed to the fore by NHLBI's Bob Balaban and then–CC Radiology's Nick Bryan. In 1999, it was still an idea, but it had a director, Alan Koretsky, recruited by NINDS to help oversee its realization. In 2000 and 2001—the first two years of a three-year pilot project funded by participating NIH institutes in proportion to their intramural budgets—quarters were renovated, people were recruited, committees were formed, and equipment dedicated to the imaging of small animals was secured.

Now investigators who walk through the door of the MIF will find a cornucopia of modalities optimized for imaging small rodents at high resolution: ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), posi-

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Becker's Brainchild

Nary a soul involved in the MIF does not trace the facility's origins back to Ted Becker, former NIDDK investigator and associate director for research services, who was the driving force behind the idea and creation of what in 1985 was called the In Vivo NMR Center. Says Becker: "Basically, I brought all the SDs together and asked for money." That model holds to this day. ■

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Evaluation of the NIH Human Research Subjects Protection Program: First Impressions

Michael Gottesman

For ten days in December and January, NIH itself became a research subject. Our clinical research programs were evaluated by a site visit team from the Association for the Accreditation of Human Research Protection Programs (AAHRPP) as part of a pilot program to develop and assess accreditation standards for human subjects research programs.

The evaluation team was chaired by Mark Brenner, vice president for research, Indiana University, Bloomington, and vice chancellor for research and graduate studies, Indiana University-Purdue University, Indianapolis, and included five other experts in human subjects protections, institutional officials who deal with clinical research, and a clinical investigator.

The visit afforded NIH the opportunity to receive a candid, confidential assessment of the effectiveness of our human subjects research program, and it enabled AAHRPP to begin to test out its accreditation and site-visit process.

The AAHRPP visitors sat in on the deliberations of 13 of 14 NIH Institutional Review Boards (IRBs; the NIEHS IRB will be evaluated separately). They interviewed senior officials, clinical directors, clinical investigators, and clinical research staff in the Institutes and in the Clinical Center and were impressed, they told us, by the frankness and cordiality of everyone they met at NIH.

They briefed NIH senior leadership and a combined group of Scientific Directors, Clinical Directors, and IRB chairs in separate sessions. Their preliminary report was comprehensive and thoughtful and will serve as a useful guide as we continue to work to improve our program to protect the patients in NIH clinical trials.

The AAHRPP team concluded that NIH has a vigorous and innovative clinical research program, with a strong culture of support for human subject research protections to which the NIH leadership and investigators are committed.

Because of the large number of IRBs at NIH, the visitors were able to evaluate a substantial number of clinical protocols in detail. They highlighted many best practices of individual NIH programs and were impressed overall by our standards for clinical research, training programs, and central policies and support activities, which enhance our human subjects research.

THE AAHRPP TEAM CONCLUDED THAT NIH HAS A VIGOROUS AND INNOVATIVE CLINICAL RESEARCH PROGRAM, WITH A STRONG CULTURE OF SUPPORT FOR HUMAN SUBJECT RESEARCH PROTECTIONS TO WHICH THE NIH LEADERSHIP AND INVESTIGATORS ARE COMMITTED. . . . . [BUT] THEY SAW SOME INEFFICIENCIES AND SOME VARIABILITY IN WORKLOAD AND STAFFING. . . .

They liked the fact that IRB members are generally in close contact with investigators and therefore knowledgeable about their strengths and weaknesses and can make informed decisions about the risk of specific research activities in the NIH environment.

They also suggested ways we could clarify and codify our overall policy. Given the large number of IRBs, it is not surprising that they saw some inefficiencies and some variability in workload and staffing that need attention.

Some tips on how to avoid future problems in our program were presented at the briefings, but more will follow once AAHRPP has had a chance to review the findings and make formal recommendations.

I am grateful to our clinical investigators and to the staff involved in human subjects research protections for their facilitating of this site visit. As soon as we have a more complete evaluation, we will meet with you to decide how to capitalize on this evaluation and create an even better human subjects research protection program. ■

Four Institute Directors Leave, but New NCI Director Named, as Budget Moves Forward

NIH STAYING THE COURSE INTO 2002

by Celia Hooper

At the most recent meeting of the Advisory Committee to the NIH Director, December 6, 2001, there was much talk of disasters. NIH staff had pitched in with aid to victims of the September 11 terrorism and the floods this summer in Texas—and were coping with increased security challenges here at home.

But with all the upheaval, and despite a spate of departures by institute directors, NIH itself is on a steady course, said Ruth Kirschstein. Kirschstein now holds the record for longest time served as acting director of NIH.

Kirschstein said recent changes in institute directorships were nothing out of the ordinary in numbers or reasons for the departures. Paul Sieving, the new director of NEI, arrived in 2001 to replace Carl Kupfer, the original director of NEI, who had led the institute for 30 years. Other institute directors bowing out of their positions in swift sequence were Enoch Gordis of NIAAA, Alan Leshner of NIDA, Steven Hyman of NIMH, and Richard Klausner of NCI. Gordis was retiring at age 71, after 15 years leading his institute. Each of the other departing directors, Kirschstein observed, had left to take incomparable positions elsewhere.

Klausner stepped down as the director of NCI Sept. 28. His current plans include heading a unit on "terrorism" at the National Academy of Sciences. Leshner left NIH in December to become chief executive officer of the American Association for the Advancement of Science, the publisher of *Science*. Hyman, NIMH director since April 1996, also left in December, to become the provost of Harvard University, Cambridge, Mass.

Kirschstein said searches were underway for new directors for NIAAA, NIMH, and NIDA, and she expected the White House to announce its appointee to head NCI very soon. Later that day, President Bush announced that Andrew C. von Eschenbach will be NCI's 12th director. NCI says it is expecting von Eschenbach to arrive Jan. 22.

Von Eschenbach, 60, comes to NCI from the University of Texas M. D. Anderson Cancer Center in Houston, where he was director of the Genitourinary Cancer Center and director of the Prostate Cancer Research Program.

NCI's press release says von Eschenbach has also served as vice president for academic affairs at M.D. Anderson and as executive vice president and chief academic officer, leading a faculty of almost 1,000 cancer researchers and clinicians.

Andrew von Eschenbach

He had been slated to head the American Cancer Society, but relinquished that position before starting it, in order to lead NCI. He was unable to talk to *The NIH Catalyst* prior to his arrival here toward the end of January.

In a statement released by M.D. Anderson, von Eschenbach said, "My goal for the future is to accelerate making new discoveries and delivering targeted therapies as rapidly as possible to cancer patients . . . . I am keenly aware of the need to reduce the burden of cancer for those in minority and underserved populations."

If von Eschenbach's appointment confirmed Kirschstein's reassurances, so also did Congressional passage of the HHS budget for FY 2002—reported out of conference committee on Dec. 20 and signed into law by President Bush on January 10. It provides $23.2 billion for NIH, an increase of about 15 percent over the past fiscal year. ■

NIH Library Update

The NIH Library in Building 10 offers full-text online journals and a slew of services and resources. Some of the more recent provisions follow.

■ ***Additional databases now offered through Ovid Online.*** CINAHL, AGRICOLA, MEDLINE—including PreMEDLINE from 1966 and PsycINFO with coverage from 1887—are now accessible via desktop. See **<http://nihlibrary.nih.gov/tracers/sept01news-ovid.htm>**.

■ ***E-delivery available for all document requests.*** The Library can now e-mail full-text journal articles to NIH staff who use Web of Science; submit requests via the Library's online catalog or use printed form 232. See **<http://nihlibrary.nih.gov/tracers/sept01news-edelivery.htm>**.

■ ***Loansome Doc delivery options defined.*** Users should select mail or e-mail delivery for NIH addresses only for Loansome Doc requests. Documents are not faxed. For assistance in making changes to your Loansome Doc profile, e-mail Rosalie Stroman at **<rs86o@nih.gov>**. See **<http://nihlibrary.nih.gov/tracers/sept01news-loansomedoc.htm>**.

■ ***Electronic access activated for more journals.*** American Chemical Society journals, as well as the *American Journal of Public Health* and *Immunological Investigations*, are now available electronically from the NIH Library's Online Journals page. See **<http://nihlibrary.nih.gov/tracers/sept01news-newjournals.htm>**.

■ ***NEW tutorial on ordering articles from PubMed.*** An animated PubMed tutorial with step-by-step instructions on how to register to order documents from PubMed is available at **<http://nihlibrary.nih.gov/tracers/sept01news-pubmedtutorial.htm>**.

■ ***NEW online books.*** The online version of Current Protocols laboratory manuals and links to Cytokine Reference and **<LWWOncology.com>** can be accessed from the Electronic Resources Online Books page. See **http://nihlibrary.nih.gov/tracers/sept01news-newbooks.htm>**.

■ ***NEW scientific and medical web sites.*** Three new authoritative links have been added to the NIH Library's Scientific and Medical Sites page. Access highly cited articles by category, a scientific content search engine, and global health. See **<http://nihlibrary.nih.gov/tracers/sept01news-newsites.htm>**.

For more about Library services, subscribe to the NIH Library's news alert e-mail service by e-mailing **<LISTSERV@LIST.NIH.GOV>** with the message: subscribe NIHLIB-L your name. To unsubscribe, use the message: unsubscribe NIHLIB-L. E-mail **<NIHLIBRARY@NIH.GOV>** or call 301-496-2184 with comments. ■

Griff Rodgers
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material—an outgrowth of SCD research he laughingly calls an "aside."

Counting the Shoulders

Rodgers cannot describe his sickle cell research without enumerating the achievements of others that informed his own visions. "When I arrived on the scene," he says, "a number of factors had converged to allow for the discovery of the value of hydroxyurea."

There was already a body of epidemiological literature that clearly suggested that high levels of fetal hemoglobin—conferred, like sickle cell itself, through mutation—were protective against the clinical manifestation of SCD.

The work of a dermatology professor at Rodgers' medical school who used a chemotherapeutic agent to establish what appeared to be normal skin structure and function in patients with psoriasis invited the notion that a drug that decreased the rate of cell proliferation could be of benefit in nonmalignant diseases that were nonetheless characterized by rapid cell turnover—such as SCD.

A small but statistically significant and reproducible rise in fetal hemoglobin levels observed in cancer patients on chemotherapy suggested that fetal hemoglobin levels could indeed be manipulated pharmacologically.

Studies in rhesus macaques, which resemble humans in having fetal and adult hemoglobin systems, demonstrated proof of concept that the fetal hemoglobin gene could be turned back on by chemotherapeutic agents (in this case, 5-azacytidine).

Clinical studies at the University of Illinois and at the NIH Clinical Center (CC) showed that the same drug could do the same thing in SCD patients.

But the potential adverse effects of 5-azacytidine would preclude its long-term use. So it was in the testing of hydroxyurea as a less toxic and more effective alternative to 5-azacytidine that Rodgers took his place in the research chain of events, he says.

In this endeavor, he gives the greatest credit to his CC patients, who were "most generous with their time," spending three to four months in the CC and enabling the researchers to ensure compliance and serially check blood counts and serum hydroxyurea levels. The 70 percent response rate, reported in 1990[1], established hydroxyurea as an agent to be pursued.

Expanding the Search

While hydroxyurea testing moved to extramural venues for the large, definitive clinical trials that would serve as the basis for FDA approval, Rodgers and his colleagues looked for reasons for the variable response to hydroxyurea and ways to enhance it in those who responded with only modest fetal hemoglobin increases.

They could discern no way to predict response to hydroxyurea, but they succeeded in improving response with the addition of growth factors to the regimen. First in primates and then in CC patients, erythropoietin (EPO) proved to be the best of the growth factors tested in augmenting fetal hemoglobin response. Fetal hemoglobin levels in modest responders to hydroxyurea alone—in the 2–8 percent range—rose to 20 percent with the addition of EPO. The findings were reported in 1993[2].

The drawback, Rodgers says, is the prohibitive cost of EPO at the doses given to change the kinetics of red cell maturation—about an order of magnitude higher than those required to restore normal hemoglobin levels in dialysis patients. "Again, we have good proof of concept, but not a practical approach," he says.

The minimum effective dose of EPO is the subject of an impending pharmaceutical company trial to be carried out at several U.S. universities. Rodgers will sit on the study's independent data safety and monitoring board.

Differential Displays

Meanwhile, the team has begun to unravel the molecular mechanisms of hydroxyurea's actions, using a liquid culture system in which they can "take a white cell component of blood and in three weeks watch it grow into red blood cells—in the presence or absence of hydroxyurea." They have found that the fetal hemoglobin levels in these cells mirror those obtained in vivo in SCD patients—in "a couple of dozen" patients thus far, not yet enough upon which to base treatment decisions.

"We are, however, confident that the underlying basis of what causes fetal hemoglobin to be induced relates to the molecular biology of the cells as they differentiate—and this is different in different groups of people," Rodgers notes, observing that this finding could have relevance to emerging hematopoietic stem cell therapies for cancer and other diseases.

Using differential display techniques, Rodgers and his colleagues take blood stem cells, treat them with hydroxyurea, and compare what genes are expressed in the absence and presence of the drug.

"We have cloned four genes differentially expressed in the presence of hydroxyurea," Rodgers notes.

The first, a small GTP-binding protein involved in protein trafficking from the endoplasmic reticulum to the Golgi, induces fetal hemoglobin expression in a human leukemia cell line.

"Either alone or in combination with any of the three other genes we've found, this GTP-binding protein might be the basis of hydroxyurea's effects," Rodgers says. Using flow cytometry, he and his colleagues have observed that the cells of patients treated with hydroxyurea tend to be arrested in S phase. Overexpression of the GTP-binding protein in these cells magnifies the drug's effects and is associated with larger size, increased fetal hemoglobin, and diminished cell doubling rate. "This gene," he says, "may have yet unimagined effects."

The team is now creating a transgenic mouse model to further characterize the GTP-binding protein and to test the effects of partner proteins on red cell kinetics.

Shifting into Reverse

In parallel with efforts to understand and augment means to express fetal hemoglobin, Rodgers is also set upon saving a particular adult form of hemoglobin from extinction.

Hemoglobin A2, which accounts for perhaps 1–2 percent of adult hemoglobin, acts much the same as fetal hemoglobin in interfering with the sickling process by inhibiting polymerization of the sickle protein. The gene that encodes A2, however, is "evolutionarily on the way to becoming a pseudogene because of mutations in its promoter," Rodgers says.

"We are trying to reverse evolution—to restore these critical pieces of mutated DNA and build a better DNA-binding motif coupled with the normal activation domain to get higher levels of transcription in transgenic models. Ultimately," he says, "we'd like to get this chimeric molecule into the stem cells of sickle cell and thalassemia patients—but that's a long way off."

In anticipation of developing useful gene-based blood stem cell strategies, Rodgers' team and collaborators in the CC Department of Transfusion Medicine have begun a project with several local hospitals to collect, store, and conduct research on cord blood from about 100 newborns with SCD. "We are optimistic that this line of investigative inquiry will yield important results relevant to adoptive stem cell therapy," Rodgers says.

Stem Cell Potentials

The techniques developed to study the effects of different agents on red blood cell development have proved "enormously valuable" in studying the question of lineage commitment in general.

"We were able to expand this system to grow adult hematopoietic cells that have the capacity to make not only red blood cells but white blood cell and platelet progenitors as well. . . . What defines lineage commitment? What is it that instructs the stem cell to become a red cell or a white cell or a platelet? The level of cytokines is one influencing factor, but there must be others," Rodgers observes.

Beyond that, animal studies have suggested that hematopoietic stem cells may have the capacity to make muscle, nerve tissue, and possibly bone. "We're exploring this area of reparative or regenerative medicine using hematopoietic stem cells," he says, noting that his research has involved adult stem cells only.

Using differential display in liquid culture, Rodgers and his colleagues have cloned ten "novel genes associated with lineage commitment, some of which appear to be expressed not only in hematopoietic development but also in gut, pancreas, and renal development—of obvious interest to an institute dedicated to research on the digestive system and kidney diseases.

"These genes," Rodgers says, "may give us some clues into the origins of certain types of cancers and developmental anomalies, and we are currently exploring this, too." ■

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2. G.P. Rodgers, G.J. Dover, N. Uyesaka, C.T. Noguchi, A.N. Schechter, and A.W. Nienhuis. "Erythropoietin augments the fetal hemoglobin response to hydroxyurea in sickle cell patients." *N. Engl. J. Med.* **328**:75–80 (1993).

'Lineage Commitment' on a Personal Level —To Integrate Basic and Clinical Research

From "the beginning"—call it high school—Griff Rodgers says, he wanted to do more than learn about science and be a physician. He wanted also to contribute to the body of scientific knowledge, and he wanted those contributions to have a direct effect on the patients he treated. For him, basic and clinical research and clinical care were indivisible, and he mapped his career path accordingly.

Fran Pollner

Griff Rodgers

In high school, he secured accelerated admission into medical school via a seven-year combined undergraduate/graduate/medical degree program offered by Brown University in Providence, R.I.

At Brown, his general desire to embrace basic research that translated into clinical benefit became focused on blood cell disorders. He worked in a lab where he evaluated function in red blood cells that were passed through a membrane oxygenator in animals receiving artificial organs. He also carried out a research project involving aspects of globin gene expression in a human erythroleukemia cell line (K562)—a cell line he would later use extensively in his sickle cell research at NIH.

During his first medical school year in 1976, he applied for a Public Health Service scholarship—a three-year scholarship with a one-year payback. Payback could have been working at a PHS hospital or in an underserved area—or doing biomedical research at NIH. For Rodgers, doing research related to patient care at a world-renowned institution was the obvious choice. Acceptance into the NIH training program, however, required more than his choosing it; it was predicated on a positive review of a grant proposal, "much like competing for an extramural grant," he notes.

The terms of the PHS scholarship allowed for the completion of a full clinical residency before embarking on training in research at NIH. Rogers completed his residency training, including a chief residency, at Washington University in St. Louis, where his work with hematologists doing sickle cell disease research solidified his own interest.

Rodgers interviewed at several different NIH laboratories, seeking a lab that was involved in both basic research related to red cell gene expression and clinical research on sickle cell disease. He chose the NIDDK Laboratory of Chemical Biology, where, under lab chief Alan Schechter, he advanced through the ranks from fellow in 1982 to senior investigator in 1990 before becoming a unit chief and then a section chief and, in 1998, chief of the Molecular and Clinical Hematology Branch, a position he retained after he became NIDDK deputy director last year.

Rodgers was a charter member of the NIH Central Tenure Committee and the Clinical Center Board of Governors. He currently sits on the Board of Tutors of the Clinical Research Training Program, and the NIH-Duke Masters in Clinical Research Admissions Committee. He's a member of the subspeciality board on hematology for the American Board of Internal Medicine and of a national advisory committee for the Robert Wood Johnson Foundation. ■

The Talk of the Town: Security at NIH

by Fran Pollner

In the wake of September 11, security guards have become as much of the ambience at NIH as excavation pits; and needing to prove daily that one is a legitimate denizen of the NIH community has taken its place among the common gripes, much like not being able to find a parking space.

But unlike razing parking lots to make way for new laboratory buildings—generally accepted as a bothersome but necessary price to pay for expansion of research facilities—the risk-benefit ratio and appropriateness of the security measures undertaken here have been the subject of many a private debate among colleagues.

That debate was given a public airing the days preceding Thanksgiving: A series of town meetings on "safety & security at the NIH" featured Steve Ficca, ORS director, presenting an overview of the current and changing security scenario, followed by a lengthy question-and-answer session, with questions fielded by Ficca and a panel of involved NIH staff.

Objectives, Perceived Risks, Actions and Action Plans

The objective of preserving the safety and security of NIH—its people, intellectual property, and facilities—without impeding the research mission of NIH or its open and collegial atmosphere has remained constant from the day NIH was established to the present moment. Before and after September 11, there is no difference in the objective, Ficca said; it's the environment that has changed.

The perception that NIH is a potential terrorist target by virtue of the research it conducts and as a source of agents that could be weaponized is larger than the reality, Ficca said. NIH has always been a visible site for activist groups to stage protests—animal rights and AIDS-related demonstrations, for example—and it also has its share of daily petty thefts. Moreover, the Bethesda campus typically accommodates about 5,000 visitors daily. Although it's difficult to determine the extent of increased risk to NIH posed by the events of September 11, NIH, like other government facilities, was ordered to go "rapidly from low-level to high-level security" status.

There have been no drastic changes in infrastructure, as there might well be under the highest security alert, but steps have been taken to control access to the campus perimeters and building entrances. Inspection of non-NIH vehicles, random inspection of NIH vehicles, the issuing of visitor IDs and checking of employee IDs, and baggage inspection have all become part of campus life. The idea, Ficca said, is to be effective without being obstructive.

The NIH mail facility has been tested, and the mail is being screened; UPS and FedEx are being screened "at the perimeter." Community activities on the Bethesda campus have been curtailed.

Additional actions planned are the building of a fence around the campus perimeter to control pedestrian access, as well as improved electronic control of access to buildings. "There will be a change in the key card system, probably by June," Ficca said. Also being considered are some access controls within buildings, a visitors' processing and information center somewhere on the campus perimeter, a clearing facility for delivered goods, and an appraisal of risk vulnerability of campus buildings with commensurate security improvements, such as establishing a central receiving area for certain buildings.

Complaints

Audience comments and questions revealed that among those concerned enough to speak at the town meeting, complaints ran high. On one hand, there were those who felt that security was inconsistent and inadequate; on the other were those who felt it was excessive and offensive.

Some people expressed dismay that the gym in building 10 was still closed after-hours, unlike that in Building 31, which reopened. Because Building 10 houses the Clinical Center, it's open and under 24-hour security watch. Because monitoring every corner of activity is quite demanding and requires a lot of manpower, the nonessential corners have been cut.

"We are doing everything to allow activities to proceed that occur during normal hours and are in keeping with the NIH mission," such as the Research Festival in October, which involved a lot of "behind the scenes" security work, said Leonard Taylor, ORS deputy director. As for off-hours activities, a "sliding scale of event priorities" has been established: Staff training would have a high priority, but less relevant activities not directly tied to the NIH mission would not, he said.

Several people focused on the problems posed by curtailed bus and shuttle services and blocked entrances and parking lots—another area where officials are evaluating how to ameliorate the inconveniences.

One person was applauded after he decried the "waste of resources" in subjecting people who have worked here for years to "airport"-type searches every time they enter certain buildings.

"The vigilance in Building 10 must be extreme," Taylor commented. "The foot traffic is enormous in this major federal hospital facility." NIH chief of police Al Hinton noted that weapons had been confiscated during what have become routine searches.

These responses called forth the declaration from an NIH veteran of 18 years that he "thoroughly disagree(s) with everything that's been done here since September 11." He called the security procedures a "daily indignity" that holds everyone on campus "guilty until proven innocent."

Michael Gottesman, deputy director for intramural research, observed that there are "many here who are terrified by the prospect of terrorism" and that without a certain level of security, some would not work here.

Another scientist cautioned that security procedures were so obstructive they might hamper the recruitment of scientists; she noted, too, that access to seminars in some of the smaller buildings by people without card keys had become very difficult. She compared the situation at the Bethesda campus—where one has to go through security checks, including belongings, just to visit other scientists in different buildings—to that at NCI's Frederick facility, where, she said, security procedures occur at the perimeter only and are therefore less obstructionist.

Ficca promised that future improvements would alleviate that burden. No one could say whether the daily routine at NIH would ever return to the pre-September 11th normal.

In Case of Concerns

NIH Chief of Police Al Hinton invited anyone in the NIH community with security-related concerns to call him at 301-496-2387.

SD and ACD Briefings

The scientific directors (SDs) got a security update during their regular biweekly meeting in early December. ORS deputy director Leonard Taylor reported much the same sort of information released at the town meetings and confirmed that there will be a fence around the Bethesda campus perimeter—the better to screen out unfriendly individuals and objects and therefore to lighten the burden of repeated security checks within campus borders.

Taylor noted that much of what has transpired at NIH reflects compliance with government-wide prescriptions for protecting civilian federal facilities. Whether these security measures have had a deterrent effect is a difficult achievement to prove, he observed.

Security measures may well become less visible and intrusive, but, acting NIH director Ruth Kirschstein told the Advisory Committee to the Director (ACD) of NIH at its semiannual meeting December 6, "life at NIH will never be the same as it was before September 11."

Referring to the inspections committee members had undoubtedly experienced upon their arrival here, Kirschstein summed up the changes that had taken place since the ACD had last gathered on the NIH campus in June.

She noted that at least one lesson was learned from the World Trade Center disaster and earlier last summer from Tropical Storm Allison and ensuing floods at Baylor College of Medicine and other facilities in Houston: Data backup in a separate physical location is critical to recovery from such events.

Emergency preparedness has become a priority topic not only in the NIH intramural program but in the extramural community as well, ACD members attested. ■

Bioterrorism Forum at NIH

Fran Pollner

Above: *(left to right) CC director John Gallin, then-NIMH director Steve Hyman, and NIAID director Tony Fauci confer in the few minutes before the special grand rounds on bioterrorism held here October 31. Fauci discussed the "bio" in "bioterrorism," and Hyman discussed the "terror."* ***Left:*** *Fauci fields questions from the press at the end of the session. Since September 11, Fauci has been called upon repeatedly to brief officials and the public on matters related to bioterrorism, the prevention and treatment of diseases such as anthrax and smallpox, and the NIH role in activities to protect the public from these threats.*

Fellows Workshops: After NIH, What Next?

A workshop on teaching called "Success in the Classroom" will be held **February 25**, another in a series of "Survival Skills Workshops" sponsored by the NIH Fellows Committee, in conjunction with the NIH Office of Education and the Office of Research on Women's Health.

Participants will learn the basics of course design, such as selecting a textbook, developing a syllabus, and designing exams.

The next workshop, **March 18**, is on "Career Options," and will feature outside speakers on the options available after training in research, such as teaching, science law, publishing, administration, and research in industry.

Workshops are open to all NIH fellows and are held in Building 10, Lipsett Auditorium, from 8:30–11:30 a.m. No need to pr-eregister.

For more info, contact Debbie Cohen at **<dec@helix.nih.gov>** or Margaret Mentink-Kane at (301) 594-2345 or **<mmentink@niaid.nih.gov>**. ■

Mouse Imaging facility
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tron emission tomography (PET), and laser Doppler. A luciferase imager is on order.

MRI, however, is the modality "nearest and dearest" to his heart, says Koretsky, who also directs the MIF parent facility, the NIH MRI Research Facility (NMRF); he is also chief of the Laboratory of Functional and Molecular Imaging, NINDS, which has its own small animal MRI resources. Koretsky heads two ongoing protocols—one exploring cellular energy metabolism in the rat liver, heart, and brain and the other imaging brain function in rats and mice.

These two are among 30 animal studies in progress in the NMR Center, about one-third of which involve mice and rats. It was anticipated that some mouse studies begun in the center's 4.7-tesla MRI would be moved to the MIF's new 7-tesla machine.

In a progress report to the scientific directors late last year, Koretsky announced that the MIF would indeed be operational the first month of the new year, and he showcased some examples of MRI studies:

- Serial tracking of inducible lung cancer in a mutant mouse model (Galen Fisher, NHGRI, and Marty Lizak, MIF; see Figure 2, page 9)
- Dynamic MRI to assess tumor neovasculature (Steve Libutti, NCI)
- Monitoring genes injected into the rat heart (Jonathan Sorger and Elliot McVeigh, NHLBI)
- Tracking macrophage infiltration into the ischemic kidney (Robert Star, NIDDK)
- Tracking the course of tagged neural stem cells (Joe Frank, CC)

The first of these—tracking lung tumors—Koretsky later observed, "is a good example of imaging that helps a sophisticated mouse molecular biology study, and it represents something that we can do routinely. The other MRI studies are in a more developmental stage."

Other MIF modalities being used by NIH investigators include high-resolution ultrasound, harnessed by NHLBI's Cecilia Lo to elucidate cardiac dynamics and embryo surgery (see Figure 1, page 9), and micro-CT, which provides superb contrast between bone, soft tissue, and fat (see Figure 3, page 9). MIF research veterinarian Brenda Klaunberg and NIDDK's Marc Reitman are developing protocols for routine regional fat determinations using CT. Also, Koretsky noted, the MIF is helping develop a microPET resource for NIH—a working prototype (ATLAS) built by the CC's Michael Green and his colleagues (see Figure 4, page 9). PET is especially useful, Koretsky said, for detecting specific molecular interactions in vivo, such as neurotransmitter receptor distribution. Once the prototype is standardized, it will be moved into the MIF, he said.

Expert advice on which modality would best serve any given research objective is part of the MIF package of resources for investigators new to the field.

Oversight of the MIF comes under the NMR Center Steering Committee, chaired by Balaban. Balaban established the MIF subcommittee, which is chaired by King Li, the new head of the CC radiology department.

In addition to the animal imaging advisory subcommittee, there are MIF subcommittees to oversee animal safety and to review research proposals for their technical feasibility and the extent to which they will require MIF resources, including imaging time, ancillary equipment, and technician support. MIF structure and procedures can be found at <**http://intranet.nmrf.nih.gov**>.

It is not the MIF's job, however, to assess the scientific merit of proposed projects or to evaluate issues related to animal experimentation—those tasks reside within each institute and, more specifically, with its SD and its animal care and use committee. Before investigators present a protocol to the MIF, they must have done the legwork to secure those approvals.

Currently, each institute supports the MIF with a share proportional to its intramural budget. Once the pilot phase of the MIF is concluded, the funding formula that has sustained the NMR Center will go into effect in the MIF: 25 percent of the total budget will continue to be based on intramural budget and 75 percent will be based on facility usage. For the NMR Center, allocations for the coming year are estimated on the basis of usage from the previous three years, but there is a good deal of flexibility based on real-time needs as they arise. Tracking historical use of the MIF is just beginning.

Koretsky believes investigators involved in the numerous mouse studies across campus will find MIF resources invaluable for analyzing a variety of phenotypes.

Li sees the MIF as a critical locus in bench-to-bedside research in the postgenomic era. The "challenge of medical imaging," he says, "is to be able to provide in vivo information at the molecular level in a spatially and temporally resolved manner. To achieve this, in vivo experiments in animal models are essential." ■

Center Stage: *The 7-tesla, 21-cm mouse-imaging MRI, late last year before the machine was actually installed*

ultrasound

microCT

The MIF has rodent surgical and physiological monitoring capabilities

mouse prep area

Tonya Hopkins, CC, monitors MRI tracings

Mouse holding area: two laminar flow rooms hold 95 cages; animals may remain for a few days only.

photos by fran pollner

Open House

The Mouse Imaging Facility is throwing open its doors March 5 from 10 a.m. to 4 p.m. Take the main elevators in Building 10 to the B1 level, turn away from the cafeteria, and follow the signs to the door with the welcoming mouse logo. ■

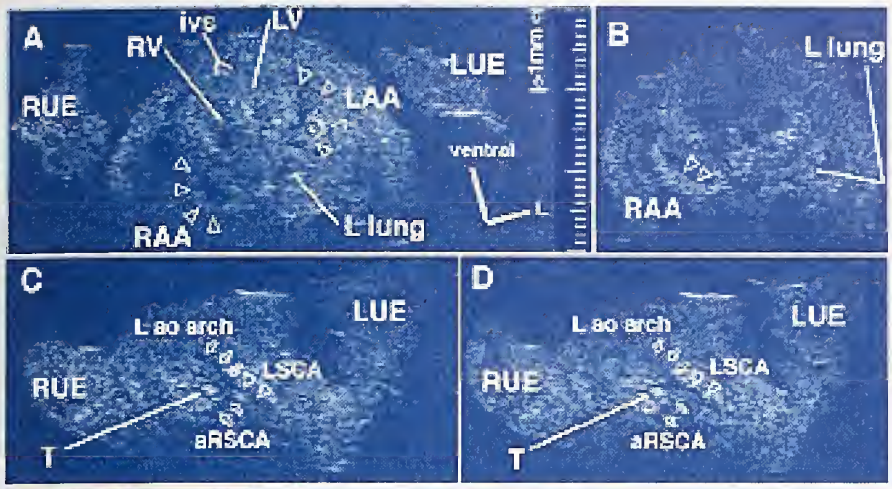
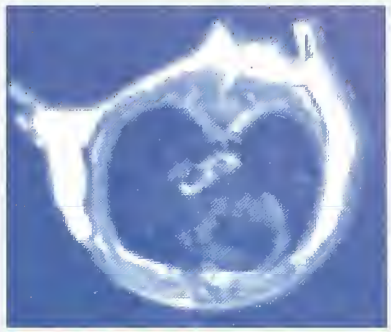
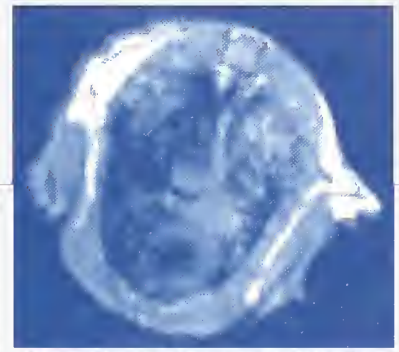


***Figure 1. Ultrasound of a Mouse Embryo**: Ultra-high-frequency (55 MHz) ultrasound imaging of an ex utero, fixed, tbx1 +/- mouse e13.5d embryo. **A.** Transverse image showing the heart within the thorax, flanked by the right (RUE) and left (LUE) forelimbs. The interventricular septum (ivs) points ventrally, resulting in the ventricular apex's appearing mesocardic at this stage. The ventricles are ventral to the atria. An echo-dense thrombus (starburst) is seen within the left atrium. The hilum of the left (L) lung can be seen. (LAA = morphologically left atrial appendage; LV = left ventricle; RAA = morphologically right atrial appendage; RV = right ventricle; 1 mm calibration is shown.) **B.** Transverse image of the heart (same embryo) slightly inferior to that in A. Pectinate muscle ridges (open arrowheads) within the morphologically right atrial appendage can now be recognized. The distal aspect of the left lung can also be seen. **C,D.** Transverse images at planes more cephalad than in A. The left aortic (L ao) arch is visualized to the left of the trachea (T). An aberrant (retro-esophageal) right subclavian artery (aRSCA) and a normal left subclavian artery (LSCA) can be identified. **E.** Sagittal imaging through the left aortic arch reveals the right (RCCA) and left (LCCA) common carotid arteries and a portion of the descending (dorsal) aorta (desc ao).*
—Cecilia Lo, NHLBI, and Alvin Chin, Children's Hospital of Philadelphia



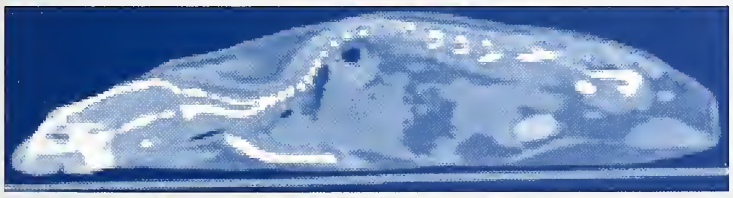
wild-type mouse with no lung tumor



lung of mutant mouse model after three months on doxycycline

the same model eight days after doxycyline withdrawal

***Figure 2. MRI of Inducible Lung Tumors**: Mutant* K-Ras *transgene whose expression could be controlled with doxycycline caused tumors in an* Ink/Arf *knockout background. The tumors regressed when the expression was switched off.*
—Galen Fisher, NHGRI, Marty Lizak, MIF, et al.
Genes and Development, *in press*



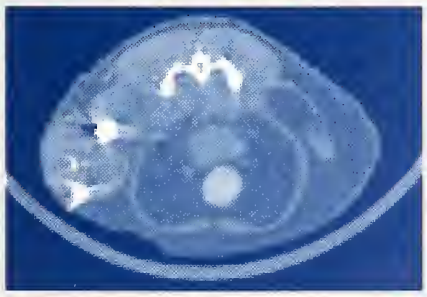


***Figure 3. X-ray Computed Tomography (CT)**: These images of a mouse were acquired at ~100 micrometer resolution. CT images are excellent for characterizing bone (brightest intensity), organ size and distribution (intermediate intensity), and regional fat (lowest intensity).*
—Brenda Klaunberg and Alan Olson, MIF

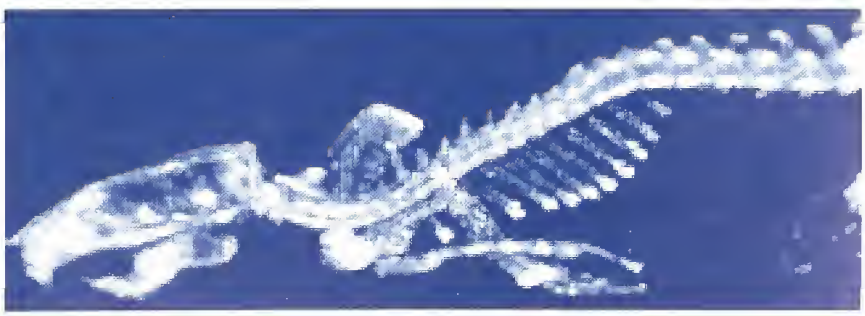


***Figure 4. Micro-PET**: Whole-body re-projection image of the rat skeleton two hours after intravenous administration of F-18 fluoride, a bone-seeking PET radiopharmaceutical. The full 3-D tomographic image set from which this image was synthesized was obtained with ATLAS, a small animal PET scanner designed and fabricated at NIH.*
—Mike Green, CC

Recently Tenured

Martin Brechbiel *received his Ph.D. from the American University in Washington, D.C., in 1988 after having joined the Radioimmune and Inorganic Chemistry Section, NCI, in 1983, where he is now a senior investigator and section chief.*

My interests are in metal chelating agents used in medicinal chemistry. My primary focus is on the design, synthesis, and evaluation of bifunctional chelating agents for sequestering metallic radionuclides in vivo. My research at NCI has applied these interests to create useful reagents and methodologies that can be translated directly into clinical trials for performing tumor-targeted imaging (γ-scintigraphy, SPECT, PET) in conjunction with targeting particle-emitting therapeutic radionuclides (β- and α-emitters).

Fran Pollner

Martin Brechbiel

We have been studying the preclinical and clinical potential of the chelating agents created in our lab with the array of available radionuclides. We primarily use monoclonal antibody radioimmunoconjugates to target the agents. Parallel to this research is a complementary area of interest stemming from the fact that many of the chelators created for radionuclides are of equal utility for complexing Gd(III). This permits the simultaneous creation of novel MRI contrast agents.

In my early work at NIH, my colleagues and I created numerous radioimmunoconjugates using bifunctional acyclic and macrocyclic chelating agents. These were evaluated in preclinical animal model studies. From these studies, we identified a DTPA derivative that proved suitable for clinical use. We used this ligand—1B4M-DTPA, also known as MX-DTPA—as the chelating agent in two clinical trials at NCI in collaboration with the Metabolism Branch and the Laboratory of Molecular Biology. This agent, commercially known as Tiuxetan, is now a component in the commercial anti-CD20 agent, Zevalin, for the treatment of non-Hodgkin's lymphoma. These advances and successes provided the platform for my subsequent and ongoing studies.

Building on what we learned from MX-DTPA, I developed methodology for the creation of the CHX DTPA family of chelating agents that have since found use at NIH and many other institutions. Of particular importance is the use of this agent in the first clinical trial with an α-emitting radionuclide, ^{213}Bi, in the treatment of acute myelogenous leukemia.

Subsequent preclinical and in vitro studies of the family of CHX DTPA chelating agents revealed a highly significant finding. The effects of stereochemistry on the in vivo stability of the metal complexes formed with radioimmunoconjugates had previously been dismissed as unimportant. We found that stereochemistry has a profound influence on complex stability that can only be detected via in vivo studies. We also recognized that this result would have to be addressed in all future studies and could be exploited to create novel agents for future applications. Examination of stereochemical components of chelating agents has since become a key aspect of my lab's work.

Carrying our chemistry forward into preclinical evaluations, we have recently initiated studies of the suitability of various particle emitters in the treatment of disseminated intraperitoneal disease. We have chosen two different model systems, pancreatic cancer and a colorectal model previously used as a model for ovarian cancer. We plan to investigate the effects of targeting multiple isotopes using at least two targeting proteins. We will also look at fractionation of dose and the inclusion of either DNA repair inhibitors and/or radiosensitizers.

Preliminary results have already revealed that the use of α-emitting radionuclides has significant therapeutic effects for the treatment of disseminated disease, permitting selective cell-by-cell targeted therapy. We now have ongoing experiments using multiple doses of ^{212}Pb and ^{212}Bi, and future studies based on the results are being planned.

In addition to targeted radiation therapies, these same chelating agents hold promise as MRI contrast agents based on polymeric dendrimeric cores. Dendrimers not only permit control of molecular size and shape but also allow large molar amounts of Gd(III) to be sequestered, thereby creating contrast agents of high relaxivity and superior contrast.

We have recently demonstrated the utility of these agents by imaging vasculature in mice. Having investigated variables of dendrimer size, character, and PEG conjugation, we have recently initiated studies to evaluate the effects of radiation on tumor vasculature. These studies can provide real-time MRI images to assess the effects of either external or systemic radiation.

We hope these parallel areas of research will be used in the clinic in the future to eradicate residual cancer cells while allowing physicians to monitor the progress of this therapy via targeted macromolecular MRI contrast agents.

Jeff Duyn *received his Ph.D. from Delft University of Technology in the Netherlands in 1988 and did postdoctoral work at the University of Trento, Italy, and the University of California at San Francisco before joining the Clinical Center in 1992. He is now a senior investigator in the Laboratory of Functional and Molecular Imaging, NINDS.*

Fran Pollner

Jeff Duyn

The main emphasis of my career has been the development of magnetic resonance (MR) methodology for the study of the human brain in vivo. My interest in this field originated in the early 1980s, when MR imaging (MRI) was just starting to show promise in the detection of pathology in humans. Since then, I have witnessed and been involved in the tremendous growth in capability and application of MR in vivo. I am intrigued and fascinated with the versatility of MRI and the great variety of contrasts that can be generated to elucidate biological processes.

During my initial years at NIH, I was involved in the development of MR spectroscopic imaging methods for the detection of metabolic abnormalities in brain infarction and brain tumors. By mapping the spatial distribution of metabolite levels and their evolution over the course of the disease, we found that metabolites such as *N*-acetyl aspartate,

choline, and lactate could serve as markers for the severity and state of disease.

Subsequently, our research focus shifted towards MRI rapid imaging techniques that detect the water signal. Specifically, we improved on techniques that could follow a bolus of contrast agent as it passed through the brain vasculature.

This work established that bolus arrival time is a sensitive marker of brain areas at risk of oxygen deprivation in patients with carotid artery disease and acute stroke. In addition, my group has designed rapid imaging techniques to detect perfusion levels without administration of contrast agents, allowing sensitive detection of the perfusion changes associated with brain activation.

More recently, we have worked on the improvement of MRI sensitivity and resolution through multichannel signal detection. Using dedicated receiver antennae that independently receive NMR signals, we found we could substantially improve sensitivity throughout the brain. This allows MRI with a spatial resolution approaching the scale of cortical columns and layers.

We expect to obtain even further improvements in MRI of human brain with the high field (7.0 tesla) MRI scanner that will be installed at NIH in 2002—only the third of its kind. It is expected to open up new avenues in the already very exciting area of brain research.

David Lovinger *received his Ph.D. from Northwestern University, Evanston, Ill., in 1987 and did postdoctoral work at NIAAA before joining the Department of Molecular Physiology and Biophysics at Vanderbilt University School of Medicine in Nashville, Tenn. He advanced to the rank of professor in that department before returning to NIAAA in February 2002 as chief of the Laboratory of Integrative Neuroscience.*

My interests are in the area of modulation and plasticity of synaptic transmission in the brain, as well as the molecular basis of acute intoxication.

One area of emphasis has been on synaptic transmission within the basal ganglia, a brain region with crucial roles in movement patterning and habit formation. My laboratory has focused especially on short- and long-term regulation of synaptic transmission at synapses connecting the cerebral cortex to the striatum (the so-called cortico-striatal synapses). These synapses constitute the entryway for information flow into the basal ganglia circuitry and are an important point for regulation of the function of the entire circuit.

David Lovinger

We have examined how neurotransmitters modulate transmission at these synapses through G-protein–coupled receptors. We have also characterized long-lasting changes in the efficacy of cortico-striatal synapses, such as long-term depression (LTD) and long-term potentiation that occur during development and can be mimicked by persistent activation of cortico-striatal inputs.

Dopamine is a key neurotransmitter in the striatum, and our studies have helped to demonstrate important roles for this neurotransmitter in striatal synaptic plasticity. We have gathered evidence indicating that striatal LTD involves a long-lasting decrease in release of the neurotransmitter glutamate from the axon terminals of cortical neurons.

The modulatory agents known as endocannabinoids coordinate communication between postsynaptic and presynaptic elements in the induction of the long-lasting decrease in transmitter release. The receptors activated by endocannabinoids are the targets of the psychoactive compounds present in marijuana and hashish. Thus, our studies are becoming intertwined with efforts to understand the mechanism of action of drugs of abuse in this brain region.

In future studies, we will continue to examine the mechanisms underlying the long-lasting decrease in synaptic function, as well as characterizing the sequence of molecular events involved in initiation of such plasticity. Ultimately, our studies may aid in the development of treatments for disorders of the basal ganglia such as Huntington's and Parkinson's diseases, and we are using animal models of these disorders to determine whether cortico-striatal transmission might be disrupted in these pathological states.

Another emphasis of research in my laboratory has been the acute actions of alcohol on ligand-gated ion channels. Work that my colleagues and I began when I was a postdoctoral fellow at NIAAA demonstrated acute actions of alcohol on different ligand-gated ion channel subtypes. These receptor channels mediate fast synaptic transmission throughout the brain, and thus their function is central to proper communication in the brain. Alcohol effects on these channels are believed to contribute to many aspects of acute intoxication.

My laboratory is interested in the role of particular subunit proteins in conferring alcohol sensitivity on the receptors. We are examining these roles in a variety of ways—from heterologous expression systems to gene-targeted mice. We hope to develop the capability in our lab to examine how these receptors and their subunits are affected by ethanol at the molecular and cellular levels. We also aim to determine the role of the receptors and subunits in acute intoxication in the behaving organism. This research may lead to new treatments of alcohol abuse and alcoholism.

Beverly Mock *received her Ph.D. from the University of Maryland, College Park, in 1983 and was a National Research Council Research Associate in the Department of Immunology at Walter Reed Army Institute of Research, Washington, D.C., before joining the Laboratory of Genetics of NCI in 1986 as a Hall-Shields Fellow. As an active member of the Mammalian Genome Society, she has been responsible for collating maps of mouse chromsome 4. She is now a senior investigator in the Laboratory of Genetics, Center for Cancer Research (CCR), NCI, and serves as CCR associate director of scientific policy.*

My research interests are concentrated on the genetics of susceptibility and resistance to cancer. I am working on mapping, cloning, and functional characterization of a set of genes involved in controlling whether certain strains of mice will, when exposed to an exogenous inducer, develop plasmacytomas—hematologic tumors of the B cell lineage. We have found that susceptibility or resistance (S or R) to this tumor is controlled by multiple genetic loci and have initiated molecular identification of these. In contrast to diseases controlled by strong gain-of-function or loss-of-function alleles, the S/R lesions in mice that develop plasmacytomas

Recently Tenured

appear to be examples of "efficiency alleles" that display relatively modest divergence from the activity of the wild-type allele.

The mouse plasmacytoma tumor system represents an excellent experimental model in which tumor S/R is inherited as a complex genetic trait. Most tumor susceptibility models in humans and in experimental animals have focused on the inherited abnormality of a single gene, such as germline mutations of *p53* or mutations of the *Apc* gene in familial polyposis of the colon and in the homologous *min* gene of the mouse. These particular single-locus lesions predispose to tumor formation because they harbor strong loss-of-function alleles. Because it is estimated that such strong germline alleles may account for only about 10 percent of human cancer, another paradigm is required to explain the other 90 percent of human cancers. Either individuals in whom these cancers arise must lack a germ-line genetic component, or tumor development in these individuals represents a complex, genetically inherited trait. Most cancers are believed to arise after exposure to environmental factors, but it is likely that genetic factors play a role in determining which exposed individuals develop tumors.

Fran Pollner

Beverly Mock

The long-term goal of my research is to elucidate the molecular and biological basis for how S/R genes determine neoplastic development. The animals we use do not have deliberately introduced genes, in contrast to transgenic and knockout or knock-in mice. Instead, we take widely used mouse strains, such as BALB/c and DBA/2, which are ostensibly normal in most respects, and analyze their genetic susceptibility and resistance to pristane-induced plasmacytomas.

The most complete part of our work has been genetic identification of multiple modifier loci that contribute to the S or R phenotype. We have used classical genetic approaches involving backcrosses of (BALB/c X DBA/2)F1 hybrids to BALB/c, genome scanning, existing congenic strains, and new congenic strains developed in our lab. The loci were then identified by correlating genotype with plasmacytoma incidence.

These studies revealed that mice harbor five or more different genes affecting susceptibility or resistance and that BALB/c is susceptible at most of these loci. Three of these loci, designated *Pctr1*, *Pctr2*, and *Pctr3*, are located on chromosome 4. We have also found that the introduction of specific oncogenes, via retroviruses, can convert DBA/2 mice from being resistant to being susceptible to pristane-induced plasmacytomas. The combination of Ras and Myc is particularly active.

We have pursued the molecular identification of the modifier loci via positional cloning as well as candidate gene approaches to test for the presence of polymorphic alleles between BALB/c and DBA/2. Using the candidate gene approach, we have shown that the *Ink4a* locus (also called *Cdkn2a*) is a candidate for this modifier locus. This gene is located within the interval to which we mapped *Pctr1*. The *Ink4a* locus is complex, as it encodes two unrelated regulatory proteins, $p16^{INK4a}$ and $p19^{ARF}$. Comparison of the coding sequences of *Ink4a* for the BALB/c alleles vs. the alleles found in most other mouse strains showed that the $p16^{INK4a}$ in BALB/c contained two missense mutations, whereas $p19^{ARF}$ in BALB/c contained a single missense mutation. Furthermore, compared with the 16^{INK4a} protein encoded by the common allele, the BALB/c $p16^{INK4a}$ protein is less efficient in binding CDK4 and inhibiting its kinase activity.

To genetically determine whether *INK4a* was a modifier locus, we bred an *Ink4a* knockout (with a genetic lesion that disrupts both $p16^{INK4a}$ and $p19^{ARF}$) onto a C57BL/6 plasmacytoma-resistant background and tested these mice for their susceptibility to pristane-induced plasmacytomas. We found that although the $p16^{INK4a}/p19^{ARF}$ heterozygotes were still resistant, the mice that were homozygous null developed these tumors even faster than BALB/c mice. In addition, the *Ink4a* locus remained tightly linked to the resistant interval on chromosome 4 when the *Pctr1* interval was shortened by further congenic breeding of the resistant DBA locus on a BALB/c background.

The biological activity of the coding sequences from the BALB/c and DBA alleles for $p16^{INK4a}$ and $p19^{ARF}$ were also compared experimentally. Similar results were obtained with two different bioassays—growth inhibition of BALB/c plasmacytoma cell lines and inhibition of *ras*-induced focal transformation of NIH 3T3 cells. The BALB/c $p16^{INK4a}$ allele was less efficient than its DBA counterpart, while the efficiency of both $p19^{ARF}$ alleles was similar. These results establish *Ink4a* as the *Pctr1* modifier locus and strongly suggest that it is primarily the gene encoding $p16^{INK4a}$ that is responsible for the BALB/c locus being a susceptibility allele. Although formal proof of this hypothesis will require analysis of mice with isolated defects in only $p16^{INK4a}$ or $p19^{ARF}$, analysis of $p19^{ARF}$ in BALB/c plasmacytomas suggests this gene may not have a major role in tumor formation, because it continues to be expressed in most of these tumors.

By contrast, $p16^{INK4a}$ is not expressed in the majority of the plasmacytomas, which is consistent with the in vitro studies noted above, indicating that the BALB/c allele possesses some biological activity. To this end, we have also observed sequence variation in the promoter region of p16 and have identified a transcription factor that may influence the expression of the protein in susceptible vs. resistant strains of mice. Taken together, the results establish that the *Pctr1* modifier locus in BALB/c represents an efficiency locus, rather than a strong gain- or loss-of-function locus as described for many familial cancer syndromes.

In addition, we are currently evaluating the candidacy of a kinase involved in detecting DNA damage for the *Pctr2* locus. Once again, a single base pair change affects the efficiency of the protein in BALB/c compared with DBA/2. These observations have led us to propose that the other modifier loci will also turn out to be efficiency alleles of pathways that are critical for pristane-induced plasmacytomas. By extension, we speculate that many human cancers will prove to be complex genetic traits determined by analogous efficiency alleles.

Jerrel Yakel *received his Ph.D. from the University of California–Los Angeles in 1988 and did postdoctoral work at the École Normale Supérieure (Paris, France)*

and Vollum Institute (Portland, Oregon) before joining the Laboratory of Cellular and Molecular Pharmacology of NIEHS in 1993. He is now a senior investigator in the Laboratory of Signal Transduction, NIEHS.

Jerrel Yakel

My interests are in the area of neuronal communication at the synapse, where the neurotransmitter released by the presynaptic terminal diffuses across the synaptic cleft and binds to and activates various ligand-gated ion channels on the postsynaptic membrane. My research at NIEHS has focused on the nicotinic acetylcholine receptor (nAChR) and the serotonin 5-HT_3 receptor channel, both of which are known to mediate rapid (on the order of milliseconds) synaptic transmission in the brain. Changes in the function of these channels have profound effects on neuronal excitability and synaptic plasticity of the cell and learning and memory in the organism. Dysfunction in these channels has been linked to various neurological diseases, such as Alzheimer's, Parkinson's, epilepsy, schizophrenia, and depression.

Nicotine is one of the most prevalent and potent neurotoxins to which we are exposed. Exposure to nicotine in utero or in early childhood has been implicated in a variety of developmental abnormalities, including brain damage and cognitive impairment. Interestingly, in adults, particularly patients with Alzheimer's disease who have been shown to express significantly fewer nAChRs in the brain, nicotine may have positive physiological effects, such as enhancing cognition and alleviating some symptoms of Alzheimer's disease. Nicotine exerts all its actions in the brain by acting on the nAChR.

To better understand the basic mechanisms and regulation of neuronal excitability by nAChRs and 5-HT_3 receptors, my lab is focusing on the function and regulation of these channels in the hippocampus, a region of the brain known to be important for learning and memory. In 1997, my colleagues and I first identified the selective expression of functional nAChRs on a subset of neurons within the hippocampus—the hippocampal interneurons. Hippocampal interneurons are inhibitory because they are known to release the inhibitory neurotransmitter GABA. A single interneuron can innervate and regulate the activity of hundreds of excitatory cells in the hippocampus. Although the nAChR and 5-HT_3 receptor channels are known to be involved in a variety of physiological processes, the precise nature of these actions is not currently known and is the major focus of investigation in my lab.

Using a variety of physiological and molecular techniques, we have been investigating which of many known nAChR and 5-HT_3 receptor subunits are forming functional channels in the hippocampus. We are also investigating whether the subunits from these two neurotransmitter receptor channels co-assemble into a single, novel type of ligand-gated channel. In 1999, my colleagues and I were the first to discover that nAChR and 5-HT_3 receptor subunits can co-assemble in heterologous expression systems, and our recent data suggest that such an interaction may be occurring in the hippocampus. Such information is extremely important in understanding the role of these channels in the brain.

Alzheimer's disease, a neurodegenerative disorder that is the leading cause of dementia, affects an estimated 4 million persons in the United States and 15 million worldwide at a staggering cost, both in quality of life and in medical care. Further, with the aging of the population, the prevalence and impact of neurodegenerative diseases such as Alzheimer's are expected to increase dramatically. Alzheimer's disease is characterized by the extensive accumulation in the brain of the β-amyloid peptide ($A\beta_{1-42}$), the formation of senile plaques, and a progressive loss of cognitive function. Whether $A\beta_{1-42}$ leads to the loss of cognitive function, and what the mechanism involved in such action might be, is unknown.

My colleagues and I recently discovered that $A\beta_{1-42}$ directly inhibits nAChRs in the hippocampus, an effect that might help to explain the cognitive deficits associated with Alzheimer's disease and lead to the development of therapeutic agents to treat patients with this condition. ■

The Catalyst *Wants You!*

The NIH Catalyst, the research news publication for and about the NIH intramural community, seeks a few good interns (one or two at any given time).

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Anyone interested in exploring an alternative career in science writing or in acquiring new skills should consider a detail to work on the *Catalyst.*

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Arrangements for those who want to straddle their lab and the *Catalyst* office are also easily made, as are accommodations for those who want to continue basically full time in the lab and fulfill discrete assignments for the *Catalyst.* Contact Fran Pollner (<**pollnerf@od.nih.gov**>; 301-402-7248). ■

New FAES Course: Demystifying Clinical Medicine for Ph.D. Scientists

Demystifying Medicine for Ph.D. Students, Fellows, and Staff," a new course offered at the FAES Graduate School (Medi 552), is based on a successful similar venture developed and conducted by Win Arias at Tufts School of Medicine in Medford, Mass., for the past 15 years. The course will begin on January 29th and continue twice weekly (Tuesday and Thursday 4:00–5:30 p.m.) until mid-May. Enrollment is limited to 170 students (who must have a Ph.D. or be in a Ph.D. program). Registration is required.

The goal is to "demystify medicine" for basic scientists through clinical presentations of patients, their pathology, and the diagnostic and therapeutic advances relevant to their cases that are linked to advances in basic biology. The course will be conducted by clinical and basic scientists and directed by Arias, who is currently an NIH Fogarty Scholar (see "A Win-Win Situation," *The NIH Catalyst*, September-October 2001, page 15).

Win Arias

The curriculum includes approximately 20 major diseases and related basic biologic advances. A **tentative schedule** appears below and at <**http://www.faes.org/medi552.htm**>.)

The course is designed to bridge the ever-increasing gap between advances in basic biology and their application to human disease. Typically, Ph.D. scientists do not receive training in pathobiology and have little understanding of clinical disease, advances in diagnosis and therapy, and the major unsolved clinical problems that challenge basic research.

Not only is learning its own excuse for being, but there is also a practical aspect to taking this course. Because of the decline in physician-scientists, more tenure-track positions in clinical departments in many of the nation's best medical schools are available for Ph.D. scientists with the clinical background offered in a course like this.

In such academic settings, Ph.D. scientists work with rather than for physician-scientists. One third of the graduates of the one-semester course in Pathobiology at Tufts have tenure-track positions in outstanding clinical departments (and most others have traditional academic and industrial positions).

For more information, contact Arias at <**iarias@helix.nih.gov**>.

Jan. 29 Jan. 31	T Th	Masur Bldg. 50	Steve Holland John Robbins	Global Infections Vaccines To Prevent Them
Feb. 4 Feb. 7	T Th	Masur Bldg.50	Cliff Lane John Coffin	AIDS: The Disease HIV: The Virus
Feb. 11 Feb. 14	T Th	Masur Bldg. 50	Toren Finkel Brian Brewer	Atherosclerosis: the #1 Disease Cholesterol Biology: The Good and the Bad
Feb. 19 Feb. 21	T Th	Masur Bldg. 50	Bob Balaban Bob Adelstein	Cardiac Diagnosis in the 21st Century Myosins: Essential Components
Feb. 26 Feb. 28	T Th	Masur Bldg. 50	Joel Moss Joel Moss	The Major Lung Diseases Genetics of Lung Disease
Mar. 5 Mar. 7	T Th	Masur Bldg. 50	Bill Gahl Juan Bonifacino	Lysosomal Diseases and Novel Therapies Lysosomal Biology
Mar. 12 Mar. 14	T Th	Masur Bldg. 50	Phil Gordon/Mark Reitman Ron McKay/Snorri Thorgeirsson	Diabetes and Obesity Stem Cells
Mar. 19 Mar. 21	T Th	Masur Bldg. 50	David Harlan Polly Matzinger	Transplantation Immune Recognition of Allografts
Mar. 26 Mar. 28	T Th	Bldg. 50 Bldg. 50	Warren Strober John Robbins	Inflammatory Bowel Disease The Infectious Etiology of Autoimmunity
Apr. 2 Apr. 4	T Th	Bldg. 50 Bldg. 50	Harvey Alter Joe Grisham	Hepatitis Viruses and Liver Disease Liver Regeneration
Apr. 9 Apr. 11	T Th	Bldg. 50 Bldg. 50	Jay Hoofnagle/Win Arias Curt Harris/ Snorri Thorgeirsson	Hepatocellular Cancer: The Disease Hepatocellular Cancer: Mechanisms
Apr. 16 Apr. 18	T Th	Masur Bldg. 50	Marston Linehan Tom Waldmann	Inherited and Acquired Renal Cancer Lymphoid Growth Factors: Treatment
Apr. 23 Apr. 25	T Th	Masur Bldg. 50	Alan Wayne Carole Thiele	Leukemias Cell Cycle: Biology and Therapeutic Targets
Apr. 30 May 2	T Th	Bldg. 50 Bldg. 50	Lyuba Varticovski Ira Pastan	Lymphoma Causes and Cures Immunotoxins: a Novel Therapeutic Strategy
May 7 May 9	T Th	Bldg. 50 Bldg. 50	Susan Bates Michael Gottesman	Anti-cancer Drug Resistance: A Major Issue Cellular and Molecular Mechanisms of Drug Resistance
May 14 May 16	T Th	Bldg. 50 Bldg. 50	Steve Rosenberg Lance Liotta	Immunotherapy of Melanoma Molecular and Cellular Basis of Metastasis
May 21 May 23	T Th	Bldg. 50 Bldg. 50	Rick Klausner/ Tom Cech	Role of Ph.D.s in Biomedical Research

Tech Transfer

An intro to tech transfer course (Genl 313), will be held Tuesdays from 5:30 to 7:30 p.m.. Topics include intellectual property, definitions of a patentable invention and an inventor, collaborative research, the patent application process, and patent litigation, infringement and interference. Special topics include third party considerations in natural products development.

For registration information, see the FAES Spring Catalog at <**http://www.faes.org/**>. Classes start Jan. 29 and will be held at the Office of Technology Transfer, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852.

Note: Late registration for classes at the FAES Graduate School will be accepted at the school's office (one Cloister Court/Building 60, Suite 230) until March 8 with a $10 late fee. ■

TransAtlantic D.Phil. Partnership

by Valerie McCaffrey, OE

Scholarships to pursue a doctorate at either Oxford or Cambridge University in the United Kingdom are available to student trainees through two collaborative arrangements established by the Graduate Partnership Program (GPP) at NIH—the NIH-University of Oxford Scholars in Biomedical Sciences program

<http://gpp.nih.gov/programs/oxford_uk_biomedical.html>

and the NIH-University of Cambridge Health Science Scholars program.

<http://gpp.nih.gov/programs/scholars_program.html>.

Six research scholarships are available for each of the programs.

Recipients of these awards participate in an interdisciplinary program designed to train outstanding students in various areas of biomedical research leading to a Doctor of Philosophy (D.Phil.) degree from either Oxford or Cambridge. The curriculum includes courses taught at both institutions (NIH and the respective university). Research projects are collaborative efforts between faculty here at the NIH and abroad.

Cambridge

Becoming a Mentor

All intramural investigators are eligible to collaborate in the training of a scholar (including those who are not stationed at the Bethesda campus). To serve as a mentor, the principal investigator must be supervising an independent research program at the rank of tenure-track or above.

Oxford

The best way to attract a doctoral fellow is to contact a potential collaborator at Oxford or Cambridge and create a collaborative proposal for a research project that could involve a student. Investigators should send collaborative project descriptions (one paragraph) with the links to their web pages as well as those of their collaborators at Cambridge or Oxford to Patty McCarthy at

<mccarthy@od.nih.gov>.

These projects will be advertised to the students, who will be encouraged to discuss them directly with potential mentors. It is also possible for a student to devise a course of study with a particular mentor in mind and initiate contact with that person.

Student Eligibility Requirements

To be eligible for this program, a student must be a U.S. citizen or permanent resident with a bachelor's degree from an accredited U.S. college or university. All applicants are expected to have had undergraduate preparation in biology, chemistry (both inorganic and organic), physics, and mathematics. Candidates should demonstrate outstanding academic performance and promise for a career in biomedical research. Previous laboratory research experience is also a strong qualification for this program. Students already enrolled in medical schools, as well as college graduates interested in pursuing a D.Phil., are encouraged to apply.

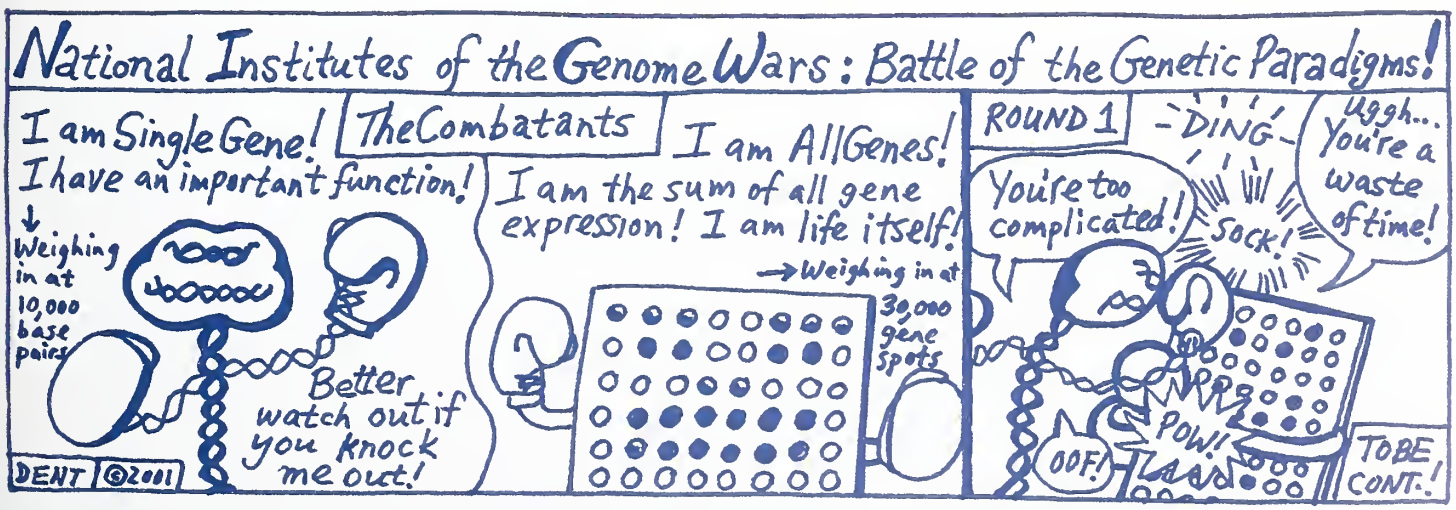
The application package should include:

- A completed form (available at **<http://www.training.nih.gov/student/index.asp>**.
- A photocopy of the official report of the Graduate Record Examination (GRE), including results from the advanced test in biology, chemistry, or biochemistry, cell and molecular biology, or the Medical College Admission Test (MCAT).
- A photocopy of the college transcript.
- Four letters of reference (at least one should be from a current or former research advisor). Letters should be in sealed envelopes bearing the signature of the person serving as reference across the seal.

For more information on this program, visit the GPP website at

<http://gpp.nih.gov>

or contact Patty McCarthy, NIH, Building 10, Room 1C129, 10 Center Drive, MSC 1158, Bethesda, MD 20892-1158, USA. Phone: 301-594-9603/9604; e-mail: **<mccarthy@od.nih.gov>**



Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: protecting research subjects, security measures at the Bethesda campus, advice for a new NIH director, and advice for the *Catalyst.*

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail: <catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2W23.

In Future Issues...

- Bench-to-Bedside: A Series
- Research Related To Public Health Threats
- Childcare Survey

1) Do you have any suggestions for improvements in the NIH Institutional Review Board process and other mechanisms to protect the patients in NIH clinical trials?

2) Assessment and readjustment of NIH security measures are ongoing. How do you feel about more recent changes and proposed future actions?

3) What do you project will be the major challenges facing a new NIH director? What do you think should be the priorities of the person who will assume NIH leadership? What advice would you give a new director?

4) As always, the *Catalyst* is interested in what you would like to see on these pages. Too much of something? Too little of other things? Any specific story or research project you'd like to see covered? Send us your suggestions.

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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